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Original Article

Hyalinizing trabecular tumor of thyroid: Does frozen section prevent unnecessarily aggressive operation? Six new cases and a literature review

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Abstract

Background: Fine-needle aspiration cytology (FNAC) is very accurate in detecting papillary thyroid carcinomas (PTCs). According to the Bethesda system for reporting thyroid cytopathology, the risk for malignancy is 97–99% when FNAC is used to diagnose PTC; the malignancy risk is 60–75% when FNAC results in suspected PTCs. The presence of hyalinizing trabecular tumor (HTT) of the thyroid can cause misdiagnosis because its cytological features mimic PTCs. However, the use of frozen section analysis can assist in the recognition of unique architecture features of HTT, and thus may help prevent the undertaking of an unnecessarily aggressive operation.
Methods: We retrospectively reviewed all patients diagnosed with HTT by permanent histopathology from February 2009 to October 2013. After acquired agreement of the patients, we analyzed all data and reviewed another nine cases of HTT reported in the English-language medical literature to examine the efficacy of frozen section.
Results: There were six patients included in our research (5 women and 1 man), with an average age of 48.8 years. Using frozen section, four patients were diagnosed with HTT and two patients were misinterpreted as PTC. Consequently, four patients had lobectomy and two patients had total thyroidectomy, with no surgical complications. Of the nine cases of HTT reviewed from the English literature, the use of frozen section showed three HTT cases, three PTC cases, two medullary thyroid carcinoma cases, and one deferral case. Overall, the use of frozen section as a diagnostic method prevented additional surgical resection in eight patients (53%).
Conclusion: Frozen section can sometimes but not always be used to diagnose HTT. When HTT is diagnosed by its trabecular pattern through the use of frozen section, it may prevent total thyroidectomy.

Keywords: frozen section; hyalinizing trabecular tumor; papillary thyroid cancer

1. Introduction

In 1987, Carney et al[1] reported 11 thyroid tumors with the following features: encapsulation, trabecular architecture with intratrabecular hyaline and colloid, polygonal and spindle cells, nuclei with frequent grooves and cytoplasmic inclusions, occasional psammoma bodies, and a low mitotic rate. The term hyalinizing trabecular adenoma was introduced to

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describe these lesions. According to the World Health Organization classification of tumors of endocrine organs, hyalinizing trabecular adenoma was redefined to describe hyalinizing trabecular tumor (HTT) as "a rare tumor of follicular cell origin with a trabecular pattern of growth and marked intratrabecular hyalinization".[2] The majority of HTTs of the thyroid are benign.[3–5] Unfortunately, there are several significant nuclear features shared by both HTT and papillary thyroid carcinoma (PTC) that make it difficult to differentiate between the two diseases by fine-needle aspiration cytology (FNAC).[6,7] The purpose of this report is to evaluate the efficacy of frozen section in intraoperative diagnosis of HTT, and to prevent misdiagnosis and subsequent surgical treatment under the misimpression of PTC.

2. Methods

After approval by our Institutional Review Board with agreement of the patients, we identified six patients with HTT (as confirmed by permanent histopathology) who had undergone thyroidectomy performed by a single surgeon from February 2009 to October 2013 at the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. All patients underwent FNAC prior to their operations and frozen section analysis during the operations. The need for thyroid operation and frozen section evaluation was prompted by suspect FNAC results, according to the Bethesda system for reporting thyroid cytopathology.[8] We analyzed the data including demographics, FNAC, frozen section results, permanent histopathology, and the extent of thyroidectomy and surgical complications. We also performed a PubMed search covering the English literature from 1990 and identified nine other cases of HTT[9] for analysis.

3. Results

Demographics, clinical presentation, FNAC, frozen section findings, and extent of thyroidectomy from our hospital study group are summarized in Table 1. All patients except one were female, and the mean patient age was 48.8 (range 29–77) years. The decision to perform total thyroidectomy ($n = 2$) or hemithyroidectomy ($n = 4$) was based on the results of the frozen section analysis. There were no complications relating to the surgical procedures. Thereafter, it was determined that four patients (66.7%) had correct intraoperative diagnosis by frozen section analysis and thus avoided total thyroidectomy.

Table 2
Summary of data in another nine patients with HTT reviewed from the English literature.

Patient	Sex/age	FNA cytology	Frozen section	Type of thyroidectomy	Permanent histopathology
1[9]	M/48	PTC	MTC	Total	HTT
2[9]	F/56	Suspicious for PTC	PTC	Total	HTT
3[9]	F/48	PTC	MTC	Total	HTT
4[9]	F/32	PTC vs. HTT	HTT	Hemi	HTT
5[9]	F/52	PTC vs. HTT	Deferred	Hemi	HTT
6[9]	F/81	Suspicious for PTC	PTC	Total	HTT
7[9]	F/38	PTC	PTC	Total	HTT
8[9]	F/26	PTC	HTT	Hemi	HTT
9[9]	F/52	PTC	HTT	Hemi	HTT

FNA = Fine-needle aspiration; HTT = hyalinizing trabecular tumor; MTC = medullary thyroid carcinoma; PTC = papillary thyroid carcinoma.

The nine cases of HTT from other series are summarized in Table 2. The use of frozen section evaluation enabled four patients (44.4%) to avoid undergoing total thyroidectomy. When combined with our six cases, an overall total of eight patients (50%) avoided undergoing an unnecessarily aggressive operation.

The FNAC of Patient Number 5 is shown in Figure 1. The nuclei were oval and slightly pleomorphic with a characteristic of overlapping and grooving, suggestive of papillary carcinoma. The frozen section (Figure 2) showed follicles of varying sizes with focal trabecular architecture and nuclei with grooves and cytoplasmic inclusions. In permanent histopathology (Figure 3), the cells were medium to large, polygonal to fusiform, arranged in trabecular patterns with the nests formed by a dense, heavily hyalinized stroma. The cells showed intranuclear cytoplasmic inclusion, nuclear grooves, and perinuclear halos mimicking papillary carcinoma.

4. Discussion

Hyalinizing trabecular tumor and PTC share significantly overlapping nuclear features and RET/PTC1 translocations. Some authors consider HTT to be a morphologic variant of PTC or a precancerous lesion.[10–12] However, recent

Table 1
Summary of data in patients with HTT in our hospital.

Patient	Sex/age	Clinical finding	FNA cytology	Frozen section	Type of thyroidectomy	Permanent histopathology
1	F/45	Graves' disease (status after subtotal thyroidectomy)	Suspicious for PTC	HTT	Near total	HTT
2	F/29	Solitary nodule	Suspicious for PTC	HTT	Hemi	HTT
3	M/52	Multiple nodular goiter, bil	Suspicious for PTC	PTC	Total	HTT
4	F/31	Solitary nodule	Suspicious for PTC	PTC	Total	HTT
5	F/59	Solitary nodule	Suspicious for PTC	HTT	Hemi	HTT
6	F/77	Solitary nodule	Suspicious for PTC	HTT	Hemi	HTT

FNA = fine-needle aspiration; HTT = hyalinizing trabecular tumor; PTC = papillary thyroid carcinoma.

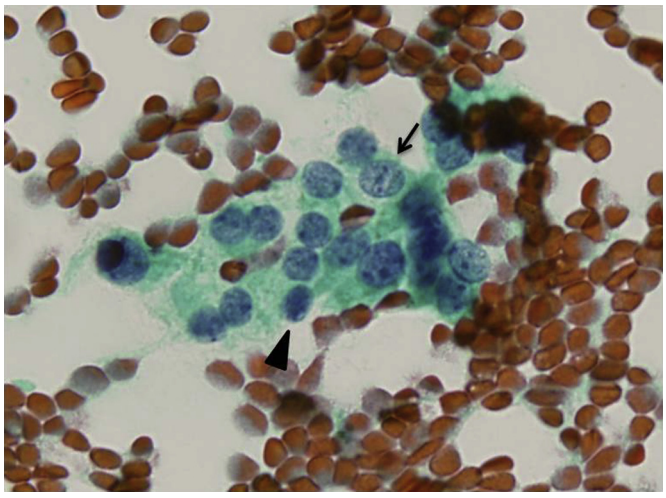

Figure 1. Cytology from fine-needle aspiration biopsy of a solitary thyroid nodule (Patient No. 5). The cytology was suspicious for papillary carcinoma. Nuclear grooves (arrow) and intranuclear cytoplasmic inclusions (arrowhead) are noted. Original magnification ×400, Papanicolaou stain.

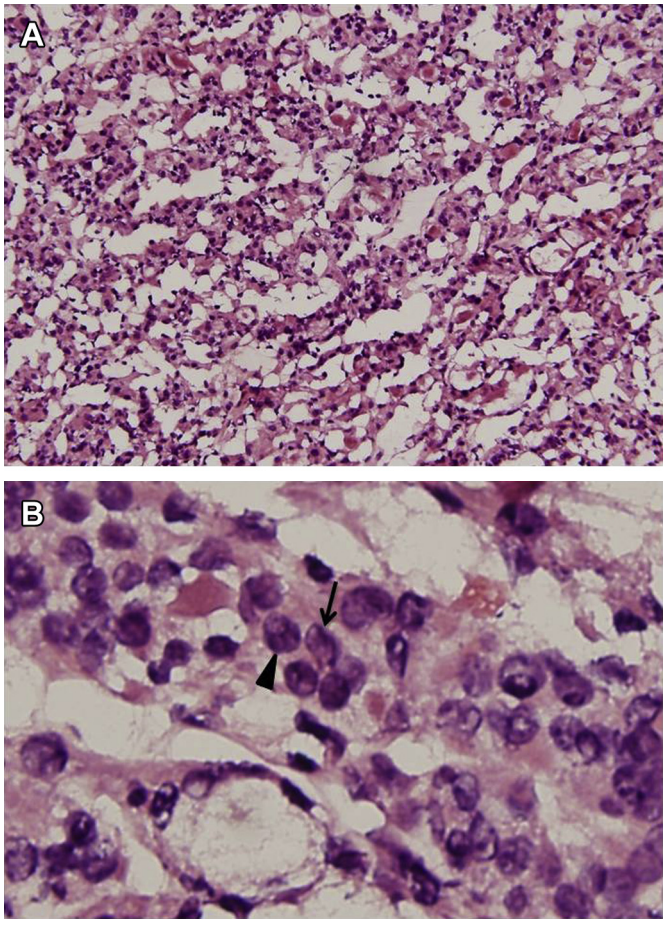

Figure 2. The frozen section of a 2.1-cm hyalinizing trabecular tumor (Patient No. 5; hematoxylin and eosin stain). (A) The cells are arranged in trabecular patterns (original magnification ×200). (B) Arrow demonstrates nuclear grooves. Arrowhead demonstrates intranuclear cytoplasmic inclusions (original magnification ×400).

investigations have shown differences in immunohistochemical staining and molecular profiles between HTT and PTC. For example, HTT has a high prevalence of RET/PTC translocations, but no B-raf or N-ras mutations.[13] In addition, there are different patterns of cytokeratin 19, high-molecular weight cytokeratin, and Galectin-3 expression in HTT and PTC. Most HTTs stained negative or weakly positive, whereas most PTCs stained strongly positive.[14,15] It was also noted that MIB-1/Ki67 cell membrane and cytoplasmic immunoreactivity is strong in HTT, but completely absent in PTC.[16] Various immunohistochemical stains and molecular profiles useful in differentiating HTT from PTC are shown in Table 3.

HTTs share some morphological and architectural similarities with medullary thyroid carcinoma (MTC), which can sometimes grow in a trabecular pattern. Amyloid deposition can be misinterpreted as hyalinizing material in frozen section; this can be confirmed by Congo red staining in permanent pathology. Additionally, serum calcitonin levels are elevated in patients with MTC.[4] Although immunochemical stain of calcitonin is diagnostic, it cannot be used in frozen section analysis.

Frozen section analysis is used to assess indeterminate lesions and to guide the surgical decision intraoperatively. However, the process of frozen section[17] may destroy or deform the hyaline, which is clear, homogeneous, and structureless, and contains water. The frozen hyaline further distorts the original cell architecture. In two of our cases, the nuclear feature and trabecular growth pattern of HTT could be identified using frozen section analysis. A false-negative result could occur if the use of frozen section showed HTT, causing the PTC, MTC, or metastatic cancers to be underdiagnosed in rare situations. In the series we have reviewed and in our cases, we all included patients with HTT diagnosed by final pathology. In the reported English literature, there are no reported cases of false-negative rate of frozen section diagnosing HTT, or patients with initially diagnosed HTT that became PTC, MTC, or metastatic cancer.

Hakata et al[18] and Strong et al[19] reported two patients with HTT (who were not included in Table 2). The use of frozen section showed MTCs, but these results were not compatible with clinical presentations and operative findings. Ultimately, the surgeon decided against total thyroidectomy.[18,19] This illustrates that when the use of frozen section cannot lead to a definitive diagnosis, a potentially two-stage operation may be an alternative. The possibility of an increased complication rate remains a concern for reoperations undertaken to remove the remaining lobe if cancer is diagnosed. However, this complication risk can be mitigated by not exploring the nonresected side of the thyroid during a patient's initial lobectomy.

Total thyroidectomy is a well-established treatment in Western countries for patients with bilateral goiters, Graves' disease, or a family history of thyroid cancer, and for RET mutation carriers.[20] However, in most Asian countries, benign thyroid lesions are not usually treated by total thyroidectomy because the clinical course is relatively benign. The recommended surgical policy tends to be conservative according to

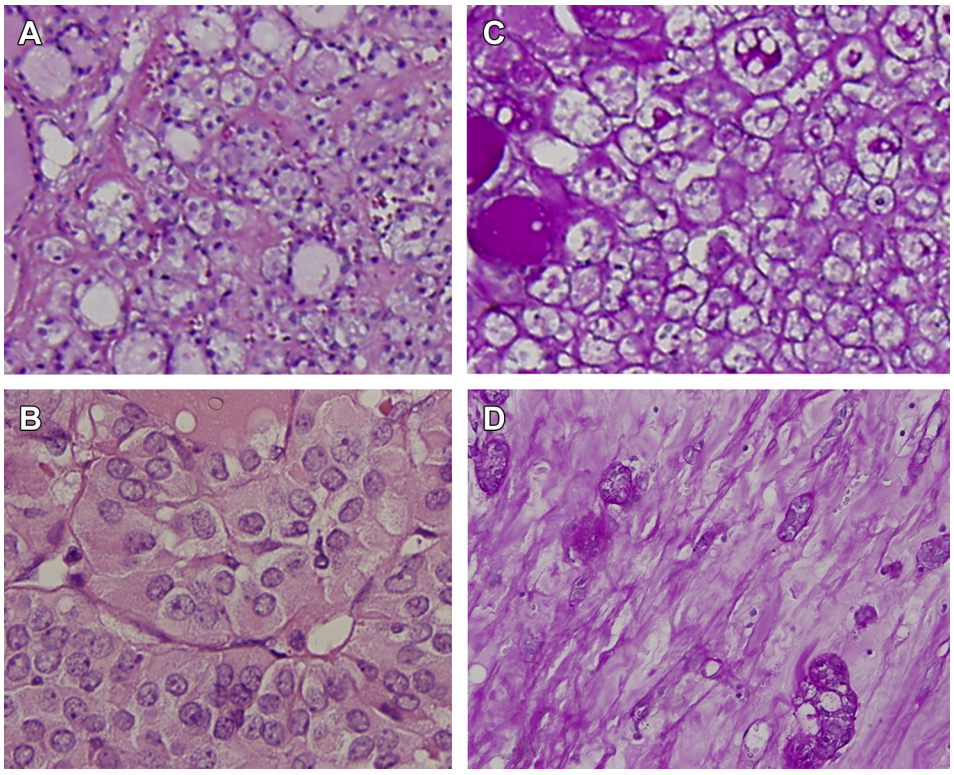

Figure 3. The permanent histopathology of the 2.1-cm HTT (Patient No. 5). (A) The cells are arranged in trabecular patterns, with nests formed by a dense, heavily hyalinized stroma (original magnification ×100). The cells are medium to large, polygonal to fusiform. (B) Intranuclear cytoplasmic inclusion, nuclear grooves, and perinuclear halos are noted (original magnification ×400). Hematoxylin and eosin stain. The intratrabecular hyaline is demonstrated with periodic acid–Schiff stain [(C) original magnification ×100; (D) original magnification ×400].

Table 3
Immunohistochemical stains and molecular profiles in differentiating HTT from PTC.

	B-raf or N-ras mutations[13]	CK-19[14]	HMCK[14]	Galectin-3[15]	MIB-1/Ki67[16]
HTT	Absent	100% − or +	100% − or +	60% − or +	90% +++
PTC	Present	100% +++	100% +++	83% +++	100% −

CK-19 = cytokeratin 19; HMCK = high-molecular weight cytokeratin; HTT = hyalinizing trabecular tumor; PTC = papillary thyroid carcinoma.

the World Health Organization and the majority of reports in the literature. However, more long-term investigations are still needed to help fine-tune the proper conduct for HTT surgical policy. It is acceptable for the surgeon to defer a total thyroidectomy procedure if the use of frozen section evaluation suggests a benign disease for patients with FNAC that indicates, but is not diagnostic of, papillary cancer; for example, if a trabecular growth pattern is found on the frozen section. Because the frozen section can be false positive or false negative, the appropriate surgical decision depends on good communication between pathologists and surgeons, and should also depend on patient preference.

In conclusion, the use of frozen section is not always diagnostic of HTT. However, when the trabecular pattern of HTT is recognized, it can spare patients from having to undergo total thyroidectomy.

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